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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,639	03/20/2002	Thomas Brodin	003300-920	7152

21839 7590 03/14/2006

BUCHANAN INGERSOLL PC
(INCLUDING BURNS, DOANE, SWECKER & MATHIS)
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
TUNGATURTHI, PARITHOSH K	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 03/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,639	BRODIN ET AL.	
	Examiner	Art Unit	
	Parithosh K. Tungaturthi	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/20/2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3 and 5-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,3,6-10 and 16* is/are allowed.

6)☒ Claim(s) *5 and 11-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/20/2005 has been entered.

2. Claims 1, 5, 11-14 have been amended.

Claims 2, 4, 34, 37 have been cancelled.

Claims 17-33, 35-36 and 38-57 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

3. Claims 1, 3, 5-16 are pending and under examination.

4. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

5. This office action contains New Grounds of Rejections.

Response to Arguments and New grounds of rejection

5. The rejection of claims 1, 3, 6-14 and 16 under 35 U.S.C.112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been withdrawn in view of amendments to the claims.

6. The applicant's reply filed on 12/20/2005 have been carefully considered and as noted in the advisory action the applicant has overcome the 102(b) of claims 1, 8 and 9; and the 103 rejection for claims 1, 3 and 6-14, in view of the amendments to the claims and the arguments presented in the reply.

7. The rejection of Claim 5 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

Claim 5 is indefinite for reciting "have an identity of at least 84% to corresponding sequences of human origin and complementary determining region (CDR) sequences" because it is not clear if the claim is drawn to an antibody wherein the 84% sequence identity corresponds to the CDR sequences.

The applicant argues that claim 5 is amended to recite "the sequences of the antibody or fragment thereof have an identity of at least 84% to corresponding sequences of human origin and complementary determining region (CDR) sequences of claim 1", to further clarify that it is the CDR sequences which have an identity of at least

84% to corresponding sequences of human origin. The applicant is reminded that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Genus*, 988 F.2d USPQ2d 1057 (Fed. Cir. 1993).

In response to this, the claim as written is still not clear if the 85% identity is towards the complementary determining region sequences or to the entire light and heavy chain of the antibody of claim 1. As written, it is impossible for one skilled in the art to determine the metes and bounds of the claim. Accordingly, the claim is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. The rejection of claim 15 is under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

The applicant argues that the recitation "other binding structures" is well known in the art as referring to other antibodies or binding entities. The arguments are carefully considered but not considered to be persuasive.

In response to this, the applicant is reminded the claims still stands unclear because it has not been shown or particularly argued as to what the "other binding structures" are. Does it mean that they bind the same antigen as the unlabeled antibody? Also, the applicant has not clearly stated what other binding structures having other binding specificities actually means. The applicant is further reminded that

as written, it is impossible for one skilled in the art to determine the metes and bounds of the claim. Accordingly, the claim is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The applicant is requested to provide evidence as to what the response states on page 11 "Applicants submit that this phrase is well known in the art as referring to other antibodies or binding entities". In that scenario, it is not clear as to what other antibodies or binding entities the applicant is referring to, in the claims. It is the examiners position, that even though the phrase "other binding structure" is well known in the art. As written, it is impossible to come to a conclusion as to what the applicant intends the invention of claim 15 to be.

9. Claims 11-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the antibody with the CDRs as specified in claim 1, does not reasonably provide enablement for an "antibody which has been genetically changed" as recited in claims 11-14. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

In the response filed on 10/20/2005, the applicant states that to over come the rejection of claims 11-14 under 35 U.S.C. 112, second paragraph, the claims are amended to recite that the antibodies are genetically changed.

The claims are drawn to an isolated antibody which has been genetically changed to: increase or decrease the avidity and/or affinity thereof, increase the

production yield thereof, influence the pharmacokinetic properties thereof and give new pharmacokinetic properties thereto. Thus, the claims broadly read on the altering the CDRs, and it is unpredictable if genetically changing the CDRs would render the antibody with the claimed properties. Further, the specification does not clearly state what and where the genetic alteration was made. These claims broadly read on amino acid substitution, deletion or insertion of any number of amino acids within the antibody sequence including the CDRs.

The claims are not commensurate in scope with the enablement provided in the specification. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions or the conformation wherein a heavy chain does not associate with a light chain may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA 1982 Vol 79 page 1979).

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin

binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252).

Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563 (1975).

In addition, Ibragimova and Eade (Biophysical Journal, Oct 1999, Vol. 77, pp. 2191-2198) teach that factors affecting protein folding and stability are governed by many small and often opposing effects and that even when the "rules" are know for altering the stability of a protein fold by the introduction of a single point mutation the result is not reliable because the balance of forces governing folding differs for different protein sequences, and that the determination of the relative magnitude of the forces governing the folding and stability of a given protein sequence is not straightforward (page 2191, first column, lines 12-17 and second column, lines 3-8).

Colman et al (Research in Immunology 1994, 145:33-36) teach the specificity of antibody-antigen interaction, wherein in one structural context, a very conservative

substitution may abolish binding; in another, a non-conservative substitution may have very little effect on the binding affinity. Current estimated of the potential number of antibody molecules that can be generated by all the known genetic mechanisms is in excess of 10^{18}. This and similar other estimates assume each of the 20 amino acids is different from every other amino acid, which is appropriate for purpose of enumeration but not for the purpose of estimating how many different antibody specificities can be produced by an animal (page 35, in particular).

These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein.

Although biotechnology has made great strides in the recent past, these references serve to demonstrate exactly how little we really know about the art. Elucidation off the genetic code induces one to believe that one can readily obtain a functional synthetic protein for any known nucleic acid sequence with predictable results. The results of the construction of synthetic proteins remain very unpredictable as Burgess et al, Lazar et al, Schwartz et al, Lin et al and Ibragimova and Eade conclusively demonstrate.

In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of derivatives encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Conclusion

10. Claims 1, 3, 6-10 and 16 are in condition for allowance.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

12. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
Parithosh K. Tungaturthi, Ph.D.
Ph: (571) 272-8789

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER